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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/683,549	10/10/2003	Fabian Somers	DI-5954 (BXTD 9004.6)	2624

321 7590 08/31/2005

SENNIGER POWERS LEAVITT AND ROEDEL
ONE METROPOLITAN SQUARE
16TH FLOOR
ST LOUIS, MO 63102

EXAMINER	
RUSSEL, JEFFREY E	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 08/31/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/683,549	SOMERS ET AL.	
	Examiner	Art Unit	
	Jeffrey E. Russel	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 August 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *16-22,24-35 and 37* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *16,17,19-22,24-35 and 37* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *10 October 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

1. Applicant's election without traverse of the species erythropoietin plus Gly-His in the reply filed on February 4, 2005 is acknowledged.

Claim 18 is withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on February 4, 2005.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

3. Claims 16, 17, 19, 21, 22, 24-26, 30-34, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Sato et al (U.S. Patent Application Publication 2003/0092622). Sato et al teach stabilized pharmaceutical compositions comprising a protein such as erythropoietin which is produced recombinantly in BHK or CHO cells and a stabilizer which is Trp or a derivative thereof in a concentration of 0.1-300 mM, preferably 1-10 mM. The EPO concentrations can range preferably from 750 to 72,000 IU/ml. The derivatives can be dipeptides such as Cbz-Gly-Trp, Cbz-Gly-Trp-OMe, Cbz-Gly-Gly-Trp-OMe, Gly-Trp, Ala-Trp, etc. The compositions are substantially free of protein stabilizers such as human serum albumin, and in the examples directed to EPO compositions, are free of protein stabilizers such as human serum albumin. The compositions can comprise a surfactant such as polysorbate 20 or 80. Surfactant concentrations are preferably 0.005-3% (w/v). The solutions are intended to be administered parenterally. See, e.g., paragraphs [0042], [0043], [0046]-[0048], [0056], [0057], and [0060]. For the dipeptide and tripeptide stabilizers mentioned above, plus others, see especially paragraph [0047], lines 21-38, 40, and 41. With respect to instant claim 34, the Trp derivatives of Sato et al are deemed to constitute "derivatives" of the specific peptide stabilizers claimed by Applicants, because of their

similarity in structure (i.e. dipeptides or tripeptides having at least one amino acid in common) and structure (i.e. ability to stabilize protein compositions). Sato et al do not teach or specifically exemplify an erythropoietin composition comprising one of the dipeptide or tripeptide stabilizers, with the composition being free (as opposed to substantially free) of serum albumin. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to use the dipeptide and tripeptide stabilizers taught by Sato et al to stabilize the erythropoietin compositions taught by Sato et al because it is desirable to stabilize erythropoietin compositions and because the dipeptide and tripeptide stabilizers taught by Sato et al would have been expected to exhibit stabilizing properties useful for the erythropoietin compositions taught by Sato et al. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to formulate the dipeptide- and tripeptide-stabilized erythropoietin compositions suggested by Sato et al so that they are free (as opposed to substantially free) of serum albumin, because it would have been prima facie obvious to omit a component which Sato et al prefer not to be present, and because it is preferable in the pharmaceutical arts to minimize the number of components in a pharmaceutical composition so as to minimize the chances of adverse side effects.

4. Claims 24-29 and 35 are rejected under 35 U.S.C. 103(a) as being obvious over Sato et al (U.S. Patent Application Publication 2003/0092622) as applied against claims 16, 17, 19, 21, 22, 24-26, 30-34, and 37 above, and further in view of the WO Patent Application 02/14356. Sato et al are not limited to stabilizing any particular type of erythropoietin, but do not teach stabilizing an erythropoietin which is erythropoietin omega. The WO Patent Application '356 teaches erythropoietin omega to be a form of erythropoietin which is useful in treating fatigue, pain,

chronic heart failure, dysrythmia and dementia. See, e.g., the Abstract; page 4, line 24 - page 9, line 14; and claim 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to stabilize the erythropoietin omega of the WO Patent Application '356 using the stabilizing agents of Sato et al because it would be desirable to stabilize the erythropoietin omega of the WO Patent Application '356 so as to preserve its therapeutic activities, and because the stabilizing agents of Sato et al have been used to preserve very closely related erythropoietin analogs and therefore would have been expected to be useful in stabilizing erythropoietin omega.

5. Claims 16, 17, 19, 21, 22, 24-26, 30-34, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/64241. The WO Patent Application '241 is equivalent to Sato et al (U.S. Patent Application Publication 2003/0092622) applied above, but is available as prior art against Applicants' claims under 35 U.S.C. 102(b). The WO Patent Application '241 suggests Applicants' claims for the same reasons that Sato et al suggest Applicants' claims.

6. Claims 24-29, and 35 are rejected under 35 U.S.C. 103(a) as being obvious over the WO Patent Application 01/64241 as applied against claims 16, 17, 19, 21, 22, 24-26, 30-34, and 37 above, and further in view of the WO Patent Application 02/14356. The WO Patent Application '241 in view of the WO Patent Application '356 suggests Applicants' claims for the same reasons that Sato et al in view of the WO Patent Application '356 suggest Applicants' claims.

7. Claims 16, 17, 19-22, 24, and 37 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608). Cormier et al disclose an aqueous composition comprising a drug which is preferably a protein or a polypeptide and a

buffer which is preferably Gly-His, at least partly in salt form. The drug can be erythropoietin. The buffer is present in a concentration of 10 mM to 1 M (2.1-212 g/L), preferably 25-250 mM (5.3-53 g/L). No serum albumin is present in the composition. See, e.g., paragraphs [0034], [0041], [0047] and claims 1, 6, and 8. Cormier et al do not specifically teach a composition comprising both erythropoietin and Gly-His, and do not teach the buffer concentration of instant claim 22. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to administer erythropoietin using the Gly-His buffer of Cormier et al because Cormier et al disclose that erythropoietin is a protein which can usefully be administered in their formulations, and because Gly-His is a preferred buffer for Cormier et al's compositions. With respect to the limitation "recombinant" in instant claim 24, process of making limitations do not impart patentability to product-by-process claims where the product is otherwise anticipated by or obvious over the prior art. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal buffer concentrations embraced by the disclosure of Cormier et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

8. Claims 24-29 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) as applied against claims 16, 17, 19-22, 24, and 37 above, and further in view of the WO Patent Application 02/14356. Cormier et al are not limited to stabilizing any particular type of erythropoietin, but do not teach stabilizing an erythropoietin which is erythropoietin omega. The WO Patent Application '356 teaches erythropoietin omega to be a form of erythropoietin which is useful in treating fatigue,

pain, chronic heart failure, dysrythmia and dementia. See, e.g., the Abstract; page 4, line 24 - page 9, line 14; and claim 1. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to formulate the erythropoietin omega of the WO Patent Application '356 in the compositions of Cormier et al because it would be desirable to administer the erythropoietin omega of the WO Patent Application '356 iontophoretically, and because the compositions of Cormier et al have been used to administer a wide range of proteins and therefore would have been expected to be useful in administering erythropoietin omega. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the erythropoietin omega to be administered in the compositions of Cormier et al as modified above by the WO Patent Application '356 because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

9. Claims 30-34 are rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) as applied against claims 16, 17, 19-22, 24, and 37 above, and further in view of Holladay et al (U.S. Patent No. 6,328,728). The compositions of Cormier et al are to be administered by transdermal electrotransport, i.e. iontophoretically (see, e.g., the Abstract, paragraph [0003], and claim 1), but Cormier et al do not teach the presence of a surface active agent in the composition comprising the protein or polypeptide. Holladay et al et al teach including a surfactant such as a polyoxyalkylene sorbitan fatty acid ester in a composition comprising a protein or polypeptide which is to be electrotransported across a body surface, i.e. across the skin. The surfactants have the benefit of increasing the flux of the protein or polypeptide across the body surface and of decreasing the

biodegradation of the proteins or polypeptides. See, e.g., column 3, line 55 - column 4, line 6, and claims 4 and 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to include a surfactant such as a polyoxyalkylene sorbitan fatty acid ester of Holladay et al in the compositions of Cormier et al so as to increase the flux and to decrease of biodegradation of the erythropoietin to be administered by Cormier et al. Note that motivation to combine under 35 U.S.C. 103 need not be the same as Applicants' expressed motivation. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the surfactants in the compositions of Cormier et al as modified above by Holladay et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

10. Claim 35 is rejected under 35 U.S.C. 103(a) as being obvious over Cormier et al (U.S. Patent Application Publication 2002/0058608) in view of the WO Patent Application 02/14356 as applied against claims 24-29 above, and further in view of Holladay et al (U.S. Patent No. 6,328,728). The compositions of Cormier et al as modified above by the WO Patent Application '356 are to be administered by transdermal electrotransport, i.e. iontophoretically (see, e.g., the Abstract, paragraph [0003], and claim 1), but Cormier et al do not teach the presence of a surface active agent in the composition comprising the protein or polypeptide. Holladay et al et al teach including a surfactant such as a polyoxyalkylene sorbitan fatty acid ester in a composition comprising a protein or polypeptide which is to be electrotransported across a body surface, i.e. across the skin. The surfactants have the benefit of increasing the flux of the protein or polypeptide across the body surface and of decreasing the biodegradation of the proteins or

polypeptides. See, e.g., column 3, line 55 - column 4, line 6, and claims 4 and 8. It would have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to include a surfactant such as a polyoxyalkylene sorbitan fatty acid ester of Holladay et al in the compositions of Cormier et al as modified above by the WO Patent Application '356 so as to increase the flux and to decrease of biodegradation of the erythropoietin omega to be administered. Note that motivation to combine under 35 U.S.C. 103 need not be the same as Applicants' expressed motivation. It would further have been obvious to one of ordinary skill in the art at the time Applicants' invention was made to determine all operable and optimal concentrations for the surfactants in the compositions of Cormier et al as modified above by the WO Patent Application '356 and Holladay et al because concentration is an art-recognized result-effective variable which is routinely determined and optimized in the pharmaceutical arts.

11. Applicant's arguments filed August 1, 2005 have been fully considered but they are not persuasive.

Sato et al (U.S. Patent Application Publication 2003/0092622) is still applied against Applicants' claims, albeit under slightly different grounds. Sato et al do teach dipeptide and tripeptide stabilizers in paragraph [0047] as cited by the examiner, more specifically at lines 21-38, 40, and 41. For example, Cbz-Gly-Trp is found at line 29 ("carbobenzyloxyglycyl tryptophan"). With respect to the possible presence of protein stabilizers such as serum albumin in the compositions of Sato et al, Applicants are correct that paragraph [0043] (and claim 10, for that matter) recites that the compositions are to be "substantially free" rather than "free" of the protein stabilizers. However, the difference between a composition which is "substantially free" of a protein stabilizer and a composition which is "free" of a protein stabilizer is minimal.

Further, in Sato et al's examples, the compositions are "free" rather than "substantially free" of protein stabilizers. Sato et al's compositions are deemed to suggest Applicants' compositions which are free of serum albumin because of the minimal difference in serum albumin concentration and because it is prima facie obvious to omit a component from the compositions of Sato et al which component Sato et al prefer not to be present.

The examiner agrees that Sato et al (U.S. Patent Application Publication 2003/0092622) is not available as prior art under 35 U.S.C. 102(e) against the instant claims. Accordingly, the equivalent publication, WO Patent Application 01/64241, is now also applied against Applicants' claims on the same basis that Sato et al is applied. The WO Patent Application '241 is available as prior art against Applicants' claims under 35 U.S.C. 102(b).

The obviousness rejection based upon Sato et al (U.S. Patent Application Publication 2003/0092622) in view of the WO Patent Application 02/14356 is maintained. Motivation for combination of the references is supplied by Sato et al, which suggests that erythropoietin in general can be stabilized with the disclosed stabilizers. The specific erythropoietin of the WO Patent Application '356 is of the type which Sato et al suggest can be stabilized.

The obviousness rejections based upon Cormier et al (U.S. Patent Application Publication 2002/0058608) as the primary reference are maintained. The examiner agrees that Cormier et al do not teach a buffered aqueous formulation containing erythropoietin. However, as the reference is not applied under 35 U.S.C. 102, this argument is not convincing. Further, because all the disclosure of a reference, and not just the reference's specific examples, must be considered in determining patentability (see MPEP 2123 and In re Snow, 176 USPQ 328 (CCPA 1973)), it is not relevant that Cormier et al do not teach exemplify erythropoietin compositions.

Applicants contend that one skilled in the art would not be motivated to formulate erythropoietin in the compositions of Cormier et al. The examiner disagrees, because Cormier et al specifically list erythropoietin as a protein which can be formulated according to their invention for transdermal electrotransport delivery. Cormier et al did not list erythropoietin for no reason; rather, Cormier et al listed erythropoietin because they intended it to be formulated according to their invention and administered transdermally. Applicants also contend that there is no reasonable expectation of success for erythropoietin formulated in the compositions of Cormier et al. However, Applicants have not provided any scientific evidence or reasoning to support this argument. Cormier et al's invention is disclosed as being generally applicable to proteins, including erythropoietin, and there is no evidence of record which would contradict this assertion of Cormier et al.

Cormier et al's discussion of histidine, as pointed out by Applicants, is noted. However, as histidine is not a peptide and is not encompassed as a stabilizer by either Cormier et al or by Applicants' claims, its use as a stabilizer for electrotransport drug formulations is not seen to be relevant to the rejections under consideration. With respect to Cormier et al and serum albumin, Cormier et al do not mention serum albumin because it is not present in their formulations. Cormier et al do not need to positively exclude components which are not present and would not have been expected to be present in their compositions.

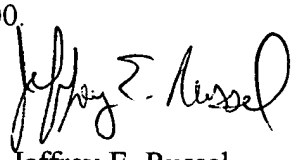
With respect to claim 37, "parenteral" is defined as "Taken into the body or administered in a manner other than through the digestive tract". See Webster's II New Riverside University Dictionary. Cormier et al's transdermal electrotransport occurs away from the digestive tract, i.e. is parenteral.

The obviousness rejection based upon Cormier et al (U.S. Patent Application Publication 2002/0058608) in view of the WO Patent Application 02/14356 is maintained. Cormier et al include erythropoietin in a list of proteins that can be administered by transdermal electrotransport when formulated in accordance with the disclosed compositions. Applicants have submitted no scientific evidence or reasoning which contradicts this assertion by Cormier et al. While the WO Patent Application '356 does not suggest transdermal administration of erythropoietin omega and does not teach or suggest formulating erythropoietin with peptide stabilizers, these differences between Applicants' claims and the WO Patent Application '356 are resolved through the combination with Cormier et al. Obviousness must be based upon a consideration of the prior art as a whole, and not upon the consideration of any single reference.

The obviousness rejection based upon Cormier et al (U.S. Patent Application Publication 2002/0058608) in view of Holladay et al (U.S. Patent No. 6,328,728) is maintained. Applicants contend that without the instant invention, one would not have had a reasonable expectation of success of achieving stabilization of erythropoietin with peptide stabilizers without the addition of serum albumin. The examiner disagrees, as neither Cormier et al (nor Sato et al or the WO Patent Application '241 applied above) disclose that serum albumin is necessary to stabilize erythropoietin. Further, it should be noted that motivation to combine references, e.g., Cormier et al and Holladay et al, need not be the same as Applicants' motivation. See MPEP 2144. If Cormier et al and Holladay et al suggest combining their references for purposes of transdermal electrotransport, this is sufficient to establish prima facie obviousness of the claimed compositions. That Applicants may formulate their compositions for purposes of erythropoietin stabilization does not rebut such a prima facie case of obviousness.

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jeffrey E. Russel at telephone number (571) 272-0969. The examiner can normally be reached on Monday-Thursday from 8:30 A.M. to 6:00 P.M. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Bruce Campell can be reached at (571) 272-0974. The fax number for formal communications to be entered into the record is (571) 273-8300; for informal communications such as proposed amendments, the fax number (571) 273-0969 can be used. The telephone number for the Technology Center 1600 receptionist is (571) 272-1600.



Jeffrey E. Russel

Primary Patent Examiner

Art Unit 1654

JRussel

August 29, 2005